Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

This submission is being made along with a Request for Continued Examination, a petition for three-month extension of time, an Information Disclosure Statement listing three references, and a Notice of Entitlement to Small Entity Status. Because this response is being timely filed, applicants respectfully request continued examination of the claims as presented herein.

Claims 1-3, 6, and 26, have been amended, claims 27 and 28 have been cancelled without prejudice, and new claims 29-32 have been introduced. Claims 1-3, 6, 26, and 29-32 remain pending.

Independent claims 1 and 26 have been amended to recite that the step of administering is carried out repeatedly to effect the desired treatment or prophylaxis of atherosclerosis. Descriptive support for this limitation is provided in the specification at Examples 1 and 2, where daily administration for four, six, eight, or twelve weeks is described. Independent claim 26 has also been amended more specifically to define the CD36 ligand as one that reduces uptake of oxidized low density lipoprotein (oxLDL). Descriptive support for this limitation appears at page 7, lines 7-16; page 8, lines 4-6; and Examples 1 and 2.

New claims 29 and 30 find descriptive support in Examples 1 and 2, where the daily administration of hexarelin or EP80317 for four or more weeks (e.g., four, six, eight, or twelve weeks) is described. Descriptive support for new claim 31 is supported at page 8, line 27 to page 9, line 5 of the application as filed. New claim 32 finds descriptive support in original claims 1 and 3; Examples 1 and 2; and page 8, line 27 to page 9, line 5 of the application as filed. Therefore, new claims 29-32 do not introduce new matter.

The rejection of claims 1-3, 6, and 26-28 under 35 U.S.C. § 112 (second paragraph) is respectfully traversed.

On pages 2-3 of the office action, the U.S. Patent and Trademark Office ("PTO") asserts that persons of skill in the art would not be apprised of the scope of the language "under conditions effective to…." Applicants respectfully disagree.

The examples in the present application demonstrate the utility of two different CD36 ligands, specifically hexarelin and EP80317, with a daily dosage of 100 μg/kg hexarelin and 300 μg/kg EP80317, respectively. These results demonstrate the efficacy and

utility of these treatments, and persons of skill in the art would be fully aware that optimization of these results can be achieved with no more than routine experimentation. Persons of skill in the art would be fully apprised of the factors that are encompassed by the "effective conditions," including, *inter alia*, frequency of administration, mode of administration, dosage, drug activity, and drug half-life. Because persons of skill in the art would fully appreciate the nature of these variables and how they can be modified to achieve the recited effect, this claim language is not indefinite.

At page 3 of the office action, the PTO asserts that claims 2 and 3 fail to narrow the scope of independent claim 1. Applicants disagree. Claim 1 encompasses a method of treatment or prophylaxis of atherosclerosis that includes "repeatedly administering one or more Growth Hormone Releasing Peptides (GHRPs) to a patient in need of such treatment or prophylaxis…." Claim 2 specifies that "the patient *is at risk of developing* atherosclerotic plaques, or cardiovascular disease associated with atherosclerosis" (emphasis introduced). Consequently, the administration "is effective to prevent development of atherosclerotic plaques, or cardiovascular diseases associated with atherosclerosis." In contrast, claim 3 specifies that "the patient *has* atherosclerotic plaques" (emphasis introduced). Consequently, the administration "is effective to cause a reduction in the area of atherosclerotic plaques." Thus, the recited patients of claims 2 and 3 are distinct of one another, and are narrower in scope than "the patient" recited in claim 1. Because claims 2 and 3 further limit the scope of claim 1, these claims are not indefinite.

For all these reasons, the rejection of claims 1-3, 6, and 26-28 for indefiniteness should be withdrawn.

The rejection of claims 26-28 under 35 U.S.C. § 112 (first paragraph) for lack of written descriptive support is rendered moot with respect to claims 27 and 28, now cancelled without prejudice, and is otherwise respectfully traversed.

Claim 26 recites a method of preventing or treating atherosclerosis that includes "repeatedly administering to a patient in need of such prevention or treatment a CD36 ligand that reduces uptake of oxidized low density lipoprotein (oxLDL), wherein said administering is carried out under conditions effective to prevent or treat atherosclerosis." Thus, this claim recites as the genus of active agents: a CD36 ligand that reduces uptake of oxidized low density lipoprotein (oxLDL). Applicants submit that this genus is fully supported by the specification and by the knowledge in the art at the time of the present invention.

The specification identifies a number of previously known GHRPs by citation to 18 prior art references on page 9, lines 5-15. In particular, the prior art identifies twelve GHRPs with GH releasing activity in WO 89/07110 and WO 89/07111; seventeen GHRPs with GH releasing activity in WO 93/04081; more than one hundred GHRP peptidomimetic compounds in WO 96/015148; twenty GHRPs with GH releasing activity in U.S. 4,411,890; and ten GHRPs that lack GH releasing activity in U.S. 6,025,471 (one of which is EP80317). Thus, the prior art demonstrates an association between the structure and function of these GHRPs.

The examples clearly correlate the observed effects of the GHRPs with their activity at CD36. Via results achieved with hexarelin and EP80317 in Examples 1 and 2, administration of the GHRPs is correlated with reduced uptake of oxLDL by CD36, and increased mRNA levels of the LXRα and ABCA1 transporter in macrophages. Because the structure-function relationship for GHRPs was well known in the art and given applicants demonstration of reduced uptake of oxLDL by CD36, persons of skill in the art would have appreciated that the applicants were in possession of the invention recited in claim 26.

Moreover, the PTO's position—that the specification fails to describe the *entire* genus of molecules—is the incorrect standard to apply. The "Guidelines for Examination of Patent Applications under the 35 U.S.C. 112 ¶ 1, 'Written Description' Requirement" make explicitly clear that the description of a representative number of species does *not* require the description to be of such a nature that it would provide support for each species that the genus embraces. 66 Fed. Reg. 1099, 1106 (2001). All that is required is a representative number of the embraced species. Given that the specification identifies hundreds of useful species and demonstrates successful results with two species of the recited genus—hexarelin and EP80317, the written description requirement is satisfied with respect to claim 26.

For these reasons, the rejection of claims 26-28 for lack of written descriptive support should be withdrawn.

The rejection of claims 1-3, 6, and 26-28 under 35 U.S.C. § 102(a) as anticipated by Broglio et al., "Effects of Acute Hexarelin Administration on Cardiac Performance in Patients with Coronary Artery Disease During By-pass Surgery," *Eur. J. Pharmacol.* 448:193-200 (2002) ("Broglio") is respectfully traversed.

Broglio discloses the use of an acute dose of hexarelin on a patient (who has coronary artery disease) during by-pass surgery. Broglio reports that hexarelin improved

cardiac function during the surgery . However, there is absolutely no disclosure whatsoever in Broglio that hexarelin can be used to treat or prevent atherosclerosis, and also lacking is any disclosure of repeated administration of hexarelin to achieve this effect. For these reasons, Broglio cannot anticipate the presently claimed invention.

Moreover, applicants submit that the claimed invention would not have been obvious over Broglio, because Broglio in no way suggests that repeated administration of hexarelin should be performed, particularly for purposes of achieving the recited effect.

For all these reasons, the rejection of claims 1-3, 6, and 26-28 as anticipated by Broglio is improper and should be withdrawn.

The rejection of claims 1-3, 6, and 26-28 under 35 U.S.C. § 102(b) as anticipated by Imbimbo et al., "Growth Hormone-releasing Activity of Hexarelin in Humans," *Eur. J. Clin. Pharmacol.* 46:421-425 (1994) ("Imbimbo"), as evidenced by the AHA Heart and Stroke Statistics 2002 Update ("AHA 2002 report"), is respectfully traversed.

Imbimbo reports on the pharmacodynamic, safety, and tolerability results of hexarelin administration to healthy male subjects. Hexarelin was administered in three separate intravenous doses, with a randomly inserted placebo dose; and all injections were separated by "one-week washout periods" (*see* Imbimbo, *study design*). Thus, each dose used in Imbimbo was effectively a single administration rather than repeated administration to achieve the presently claimed effect of treating or preventing atherosclerosis.

The PTO has cited the AHA 2002 report as evidence that 90% of the (American) population has at least one risk factor for cardiovascular disease. However, there is no suggestion or disclosure that the at least one risk factor would inevitably lead to atherosclerosis.

The PTO has taken the position that the Imbimbo must necessarily teach the presently claimed method of preventing atherosclerosis via hexarelin administration, because the AHA 2002 report would allow a person of skill in the art to reasonably assert that the 12 healthy male subjects who received the hexarelin in the Imbimbo study—presumably having at least one risk factor for cardiovascular disease—would have been treated prophylactically for atherosclerosis. Applicants disagree for several reasons.

Firstly, it is improper to infer that any of the male subjects of Imbimbo had any risk factors for atherosclerosis. While there may have been a possibility that one or more of the Imbimbo recipients may have had a risk factor, that possibility remains undetermined for the reasons asserted by applicants previously, and it is improper to conclude that it

necessarily would have been true. To assert that Imbimbo inherently anticipates the present invention, the PTO bears the burden of demonstrating that the male subjects of Imbimbo *necessarily* had a risk factor for atherosclerosis. *See In re Cruciferous Sprout Litigation v. Sunrise Farms*, 301 F.3d 1343, 1349 (Fed. Cir. 2002) (confirming that prior art must necessarily function in accordance with, or include, the claimed limitations to anticipate by inherency). All that the PTO has done is demonstrate a possibility. This is insufficient as a matter of law.

Secondly, there is likewise no basis for asserting that the administration of hexarelin in the manner described in Imbimbo inherently prevented atherosclerosis. That is because the limited doses of hexarelin—with extended 7 or 14 day "washout" periods—described by Imbimbo would not *necessarily* achieve effective results (i.e., an effective treatment of pre-existing atherosclerosis or a prophylaxis thereof). The present application provides evidence that repeated daily dosage, on the other hand, is effective.

For these reasons, the rejection of claims 1-3, 6, and 26-28 as anticipated by Imbimbo is improper and should be withdrawn.

The objection to claims 2 and 3 under 37 C.F.R. §1.75 as being a substantial duplicate of claim 1 is improper for the reasons noted above. This rejection should be withdrawn.

New claims 29-31, which are dependent on claim 1, are patentable for substantially the same reasons noted above. Moreover, both Broglio and Imbimbo are deficient because they fail to teach or suggest daily administration as recited in claims 29 and 30; or use of a GHRP that does not induce secretion of growth hormone. Therefore, claims 29-31 are clearly patentable over the cited art of record.

New claim 32 is also patentable. Neither Broglio nor Imbimbo describes therapeutic treatment of atherosclerosis, and these references certainly fail to teach or suggest (i) using a GHRP that does not induce secretion of growth hormone and (ii) daily administration thereof. Because the art is deficient in a number of respects, new claim 32 is also patentable over the art of record.

In view of all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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